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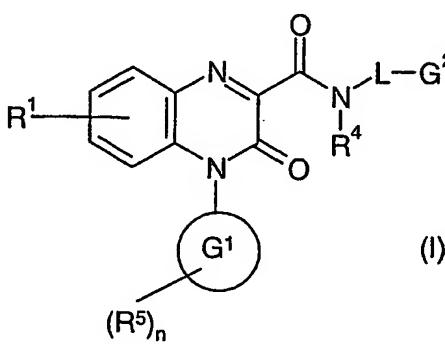
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(54) Title: QUINOXALINE DERIVATIVES AS NEUTROPHIL ELASTASE INHIBITORS AND THEIR USE



(57) Abstract: There are provided novel compounds of formula (I) wherein R¹, R⁴, R⁵, G¹, G², L and n are as defined in the Specification and optical isomers, racemates and tautomers thereof, and pharmaceutically acceptable salts thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of neutrophil elastase.

Quinoxaline derivatives as neutrophil elastase inhibitors and their use.

Field of the Invention

- 5 This invention relates to novel quinoxaline derivatives, processes for their preparation, pharmaceutical compositions comprising them, and their use in therapy.

Background of the Invention

- 10 Elastases are possibly the most destructive enzymes in the body, having the ability to degrade virtually all connective tissue components. The uncontrolled proteolytic degradation by elastases has been implicated in a number of pathological conditions. Human neutrophil elastase (hNE), a member of the chymotrypsin superfamily of serine proteases is a 33-KDa enzyme stored in the azurophilic granules of the neutrophils. In 15 neutrophils the concentration of NE exceeded 5 mM and its total cellular amount has been estimated to be up to 3 pg. Upon activation, NE is rapidly released from the granules into the extracellular space with some portion remaining bound to neutrophil plasma membrane (See Kawabat et al. 2002, Eur. J. Pharmacol. 451, 1-10). The main intracellular physiological function of NE is degradation of foreign organic molecules phagocytosed by 20 neutrophils, whereas the main target for extracellular elastase is elastin (Janoff and Scherer, 1968, J. Exp. Med. 128, 1137-1155). NE is unique, as compared to other proteases (for example, proteinase 3) in that it has the ability to degrade almost all extracellular matrix and key plasma proteins (See Kawabat et al., 2002, Eur. J. Pharmacol. 451, 1-10). It degrades a wide range of extracellular matrix proteins such as elastin, Type 3 and type 4 25 collagens, laminin, fibronectin, cytokines, etc. (Ohbayashi, H., 2002, Expert Opin. Investig. Drugs, 11, 965-980). NE is a major common mediator of many pathological changes seen in chronic lung disease including epithelial damage (Stockley, R.A. 1994, Am. J. Resp. Crit. Care Med. 150, 109-113).
- 30 The destructive role of NE was solidified almost 40 years ago when Laurell and Eriksson reported an association of chronic airflow obstruction and emphysema with deficiency of

serum α_1 -antitrypsin (Laurell and Eriksson, 1963, Scand. J. Clin. Invest. 15, 132-140). Subsequently it was determined that α_1 -antitrypsin is the most important endogenous inhibitor of human NE. The imbalance between human NE and endogenous antiprotease is believed to cause excess human NE in pulmonary tissues which is considered as a major pathogenic factor in chronic obstructive pulmonary disease (COPD). The excessive human NE shows a prominent destructive profile and actively takes part in destroying the normal pulmonary structures, followed by the irreversible enlargement of the respiratory airspaces, as seen mainly in emphysema. There is an increase in neutrophil recruitment into the lungs which is associated with increased lung elastase burden and emphysema in α_1 -proteinase inhibitor-deficient mice (Cavarra et al., 1996, Lab. Invest. 75, 273-280). Individuals with higher levels of the NE- α_1 protease inhibitor complex in bronchoalveolar lavage fluid show significantly accelerated decline in lung functions compared to those with lower levels (Betsuyaku et al. 2000, Respiration, 67, 261-267). Instillation of human NE via the trachea in rats causes lung haemorrhage, neutrophil accumulation during acute phase and emphysematous changes during chronic phase (Karaki et al., 2002, Am. J. Resp. Crit. Care Med., 166, 496-500). Studies have shown that the acute phase of pulmonary emphysema and pulmonary haemorrhage caused by NE in hamsters can be inhibited by pre-treatment with inhibitors of NE (Fujie et al., 1999, Inflamm. Res. 48, 160-167).

Neutrophil-predominant airway inflammation and mucus obstruction of the airways are major pathologic features of COPD, including cystic fibrosis and chronic bronchitis. NE impairs mucin production, leading to mucus obstruction of the airways. NE is reported to increase the expression of major respiratory mucin gene, MUC5AC (Fischer, B.M & Voynow, 2002, Am. J. Respir. Cell Biol., 26, 447-452). Aerosol administration of NE to guinea pigs produces extensive epithelial damage within 20 minutes of contact (Suzuki et al., 1996, Am. J. Resp. Crit. Care Med., 153, 1405-1411). Furthermore NE reduces the ciliary beat frequency of human respiratory epithelium *in vitro* (Smallman et al., 1984, Thorax, 39, 663-667) which is consistent with the reduced mucociliary clearance that is seen in COPD patients (Currie et al., 1984, Thorax, 42, 126-130). The instillation of NE into the airways leads to mucus gland hyperplasia in hamsters (Lucey et al., 1985, Am. Resp. Crit. Care Med., 132, 362-366). A role for NE is also implicated in mucus hypersecretion in asthma. In an allergen sensitised guinea pig acute asthma model an

inhibitor of NE prevented goblet cell degranulation and mucus hypersecretion (Nadel et al., 1999, Eur. Resp. J., 13, 190-196).

NE has been also shown to play a role in the pathogenesis of pulmonary fibrosis.

- 5 NE: α_1 -protease inhibitor complex is increased in serum of patients with pulmonary fibrosis, which correlates with the clinical parameters in these patients (Yamanouchi et al., 1998, Eur. Resp. J. 11, 120-125). In a murine model of human pulmonary fibrosis, a NE inhibitor reduced bleomycin-induced pulmonary fibrosis (Taooka et al., 1997, Am. J. Resp. Crit. Care Med., 156, 260-265). Furthermore investigators have shown that NE deficient
10 mice are resistant to bleomycin-induced pulmonary fibrosis (Dunsmore et al., 2001, Chest, 120, 35S-36S). Plasma NE level was found to be elevated in patients who progressed to ARDS implicating the importance of NE in early ARDS disease pathogenesis. (Donnelly et al., 1995, Am. J. Res. Crit. Care Med., 151, 428-1433). The antiproteases and NE complexed with antiprotease are increased in lung cancer area (Marchandise et al., 1989,
15 Eur. Resp. J. 2, 623-629). Recent studies have shown that polymorphism in the promoter region of the NE gene are associated with lung cancer development (Taniguchi et al., 2002, Clin. Cancer Res., 8, 1115-1120).

Acute lung injury caused by endotoxin in experimental animals is associated with elevated
20 levels of NE (Kawabata, et al., 1999, Am. J. Resp. Crit. Care, 161, 2013-2018). Acute lung inflammation caused by intratracheal injection of lipopolysaccharide in mice has been shown to elevate the NE activity in bronchoalveolar lavage fluid which is significantly inhibited by a NE inhibitor (Fujie et al., 1999, Eur. J. Pharmacol., 374, 117-125; Yasui, et al., 1995, Eur. Resp. J., 8, 1293-1299). NE also plays an important role in the neutrophil-induced increase of pulmonary microvascular permeability observed in a model of acute lung injury caused by tumour necrosis factor α (TNF α) and phorbol myristate acetate (PMA) in isolated perfused rabbit lungs (Miyazaki et al., 1998, Am. J. Respir. Crit. Care Med., 157, 89-94).

- 30 A role for NE has also been suggested in monocrotoline-induced pulmonary vascular wall thickening and cardiac hypertrophy (Molteni et al., 1989, Biochemical Pharmacol. 38, 2411-2419). Serine elastase inhibitor reverses the monocrotaline-induced pulmonary

hypertension and remodelling in rat pulmonary arteries (Cowan et al., 2000, Nature Medicine, 6, 698-702). Recent studies have shown that serine elastase, that is, NE or vascular elastase are important in cigarette smoke-induced muscularisation of small pulmonary arteries in guinea pigs (Wright et al., 2002, Am. J. Respir. Crit. Care Med., 166, 5 954-960).

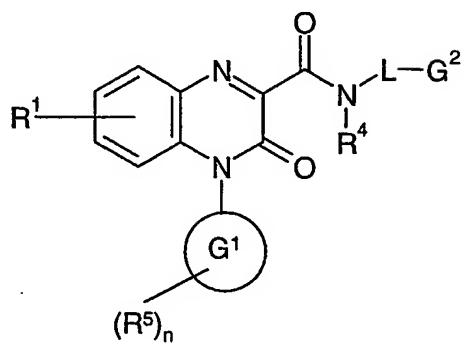
NE plays a key role in experimental cerebral ischemic damage (Shimakura et al., 2000, Brain Research, 858, 55-60), ischemia-reperfusion lung injury (Kishima et al., 1998, Ann. Thorac. Surg. 65, 913-918) and myocardial ischemia in rat heart (Tiefenbacher et al., 1997, 10 Eur. J. Physiol., 433, 563-570). Human NE levels in plasma are significantly increased above normal in inflammatory bowel diseases, for example, Crohn's disease and ulcerative colitis (Adeyemi et al., 1985, Gut, 26, 1306-1311). In addition NE has also been assumed to be involved in the pathogenesis of rheumatoid arthritis (Adeyemi et al., 1986, Rheumatol. Int., 6, 57). The development of collagen induced arthritis in mice is 15 suppressed by a NE inhibitor (Kakimoto et al., 1995, Cellular Immunol. 165, 26-32).

Thus, human NE is known as one of the most destructive serine proteases and has been implicated in a variety of inflammatory diseases. The important endogenous inhibitor of human NE is α_1 -antitrypsin. The imbalance between human NE and antiprotease is 20 believed to give rise to an excess of human NE resulting in uncontrolled tissue destruction. The protease/ antiprotease balance may be upset by a decreased availability of α_1 -antitrypsin either through inactivation by oxidants such as cigarette smoke, or as a result of genetic inability to produce sufficient serum levels. Human NE has been implicated in the promotion or exacerbation of a number of diseases such as pulmonary 25 emphysema, pulmonary fibrosis, adult respiratory distress syndrome (ARDS), ischemia reperfusion injury, rheumatoid arthritis and pulmonary hypertension.

The present invention discloses novel quinoxaline derivatives that are inhibitors of human neutrophil elastase and homologous serine proteases such as proteinase 3 and pancreatic 30 elastase, and are thereby useful in therapy.

Disclosure of the Invention

The present invention provides a compound of formula (I)



(I)

5

wherein

R^1 represents H, halogen, CN, C1 to 6 alkyl, C1 to 6 alkoxy, CO_2R^7 or CONR^8R^9 ;

10

G^1 represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N;

15

R^5 represents H, halogen, C1 to 6 alkyl, CN, C1 to 6 alkoxy, NO_2 , $\text{NR}^{14}\text{R}^{15}$, C1 to 3 alkyl substituted by one or more F atoms or C1 to 3 alkoxy substituted by one or more F atoms;

R^{14} and R^{15} independently represent H or C1 to 3 alkyl; said alkyl being optionally further substituted by one or more F atoms;

20

n represents an integer 1, 2 or 3 and when n represents 2 or 3, each R^5 group is selected independently;

R^4 represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH or C1 to 6 alkoxy;

or R^4 and L are joined together such that the group $-NR^4L$ represents a 5 to 7 membered 5 azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{16} ;

L represents a bond, O, NR^{29} or C1 to 6 alkyl; said alkyl being optionally incorporating a 10 heteroatom selected from O, S and NR^{16} ; and said alkyl being optionally further substituted by OH or OMe;

G^2 represents a monocyclic ring system selected from:

- i) phenyl or phenoxy,
- 15 ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two 20 heteroatoms independently selected from O, $S(O)_p$ and NR^{17} and optionally further incorporating a carbonyl group; or

G^2 represents a bicyclic ring system in which each of the two rings is independently selected from:

- 25 i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or

- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;
- 5 and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂,
- said monocyclic or bicyclic ring system being optionally further substituted by one to three substituents independently selected from CN, OH, C1 to 6 alkyl, C1 to 6 alkoxy, halogen,
10 NR¹⁸R¹⁹, NO₂, OSO₂R³⁸, CO₂R²⁰, C(=NH)NH₂, C(O)NR²¹R²², C(S)NR²³R²⁴,
SC(=NH)NH₂, NR³¹C(=NH)NH₂, S(O)_sR²⁵, SO₂NR²⁶R²⁷, C1 to 3 alkoxy substituted by
one or more F atoms and C1 to 3 alkyl substituted by SO₂R³⁹ or by one or more F atoms;
or
- 15 when L does not represent a bond, G² may also represent H;
- p, q, s and t independently represent an integer 0, 1 or 2;
- R⁸ and R⁹ independently represent H or C1 to 6 alkyl; or the group NR⁸R⁹ together
20 represents a 5 to 7 membered azacyclic ring optionally incorporating one further
heteroatom selected from O, S and NR²⁸;
- R¹⁸ and R¹⁹ independently represent H, C1 to 6 alkyl, formyl, C2 to 6 alkanoyl, S(O)_tR³²
25 or SO₂NR³³R³⁴; said alkyl group being optionally further substituted by halogen, CN,
C1 to 4 alkoxy or CONR⁴¹R⁴²;
- R²⁵ represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally
further substituted by one or more substituents selected independently from OH, CN,

CONR³⁵R³⁶, CO₂R³⁷, OCOR⁴⁰, C3 to 6 cycloalkyl, a C4 to 7 saturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR⁴³ and phenyl or a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N; said aromatic ring being optionally further substituted by one or more substituents selected independently from halogen, CN, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CONR⁴⁴R⁴⁵, CO₂R⁴⁶, S(O)₈R²⁵ or NHCOCH₃;

R³² represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl;

R⁷, R¹⁶, R¹⁷, R²⁰, R²¹, R²², R²³, R²⁴, R²⁶, R²⁷, R²⁸, R²⁹, R³¹, R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶ independently represent H or C1 to 6 alkyl;

and pharmaceutically acceptable salts thereof.

15

The compounds of formula (I) may exist in enantiomeric and/or tautomeric forms. It is to be understood that all enantiomers, diastereomers, racemates, tautomers and mixtures thereof are included within the scope of the invention.

- 20 Unless otherwise indicated, the term "C1 to 6 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl and hexyl. The terms "C1 to 3 alkyl" and "C1 to 4 alkyl" are to be interpreted analogously.
- 25 Examples of "C1 to 3 alkyl substituted by one or more F atoms" include fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, pentafluoroethyl and 3,3,3-trifluoropropyl.

Unless otherwise indicated, the term "C1 to 6 alkoxy" referred to herein denotes an oxygen substituent bonded to a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy and s-butoxy. The terms "C1 to 3 alkoxy" and "C1 to 4 alkoxy" are to 5 be interpreted analogously.

Examples of "C1 to 3 alkoxy substituted by one or more F atoms" include fluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy and 3,3,3-trifluoropropoxy.

10 Unless otherwise indicated, the term "C2 to 6 alkanoyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 5 carbon atoms bonded to the molecule via a carbonyl group. Examples of such groups include acetyl, propionyl and pivaloyl.

15 Unless otherwise indicated, the term "halogen" referred to herein denotes fluorine, chlorine, bromine and iodine.

20 Examples of a five or six membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N include furan, thiophene, pyrrole, oxazole, oxadiazole, isoxazole, imidazole, thiazole, triazole, thiadiazole, pyridine, pyrimidine and pyrazine.

25 Unless otherwise indicated, the term "C3 to 6 saturated or partially unsaturated cycloalkyl" referred to herein denotes a 3 to 6 membered non-aromatic carbocyclic ring optionally incorporating one or more double bonds. Examples include cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl. The term "five- or six-membered saturated or partially unsaturated cycloalkyl ring" is to be interpreted analogously.

30 Unless otherwise indicated, the term "C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group" referred to herein denotes

- a 4 to 7 membered non-aromatic heterocyclic ring optionally incorporating one or more double bonds and optionally incorporating a carbonyl group. Examples include tetrahydrofuran, thiolane 1,1-dioxide, tetrahydropyran, 4-oxo-4H-pyran, pyrrolidine, pyrrolidine, imidazolidine, 1,3-dioxolane, piperidine, piperazine, morpholine,
5 perhydroazepine, pyrrolidone and piperidone. The term "five- or six-membered saturated or partially unsaturated heterocyclic ring containing one heteroatom selected from O, S and NR¹³," is to be interpreted analogously.

Examples of a "5 to 7 membered azacyclic ring optionally incorporating one further
10 heteroatom selected from O, S and NR¹⁶," include pyrrolidine, piperidine, morpholine, thiomorpholine and piperazine.

In the definition of L, "C1 to 6 alkyl; said alkyl optionally incorporating a heteroatom selected from O, S and NR¹⁶," embraces a straight or branched chain arrangement of 1 to 6
15 carbon atoms in which any two carbon atoms are optionally separated by O, S or NR¹⁶. The definition thus includes, for example, methylene, ethylene, propylene, hexamethylene, ethylethylene, -CH₂CH₂O-CH₂- , -CH₂CH₂O-CH₂-CH₂- , -CH₂CH₂S- and -CH₂CH₂NR¹⁶-.

- 20 Examples of bicyclic ring systems in which the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂ include biphenyl, thiarylphenyl, pyrazolylphenyl, phenoxyphenyl, naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolyl, chromanyl, 25 indenyl, quinazolyl, quinoxalyl, chromanyl, isocromanyl, 3H-indolyl, 1H-indazolyl, quinuclidyl, tetrahydronaphthyl, dihydrobenzofuranyl, morpholine-4-ylphenyl, 1,3-benzodioxolyl, 1,1-dioxido-2,3-dihydro-1-benzothienyl, 2,3-dihydro-1,4-benzodioxinyl and 3,4-dihydro-isochromenyl.

In one embodiment, R¹ in formula (I) represents H.

In one embodiment, G¹ in formula (I) represents phenyl or pyridyl. In another embodiment, G¹ in formula (I) represents phenyl.

5

In one embodiment, R⁵ in formula (I) represents halogen, C1 to 6 alkyl, CN or C1 to 3 alkyl substituted by one or more F atoms. In another embodiment, R⁵ in formula (I) represents Cl, CH₃, CN or CF₃.

10 In one embodiment, n represents the integer 1.

In another embodiment, G¹ in formula (I) represents phenyl, R⁵ represents CF₃ and n represents the integer 1.

15 In one embodiment, R⁴ represents H.

In one embodiment, L represents C1 to 6 alkyl. In another embodiment, L represents -CH₂-²⁹. In another embodiment, L represents NR²⁹ and R²⁹ represents H.

20 In one embodiment, G² represents an optionally substituted monocyclic ring system selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 25 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or

- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group.
- 5 In another embodiment, G² represents optionally substituted phenyl. In another embodiment, G² represents phenyl substituted by OSO₂R³⁸, S(O)_sR²⁵, SO₂NR²⁶R²⁷, NR¹⁸R¹⁹ (wherein at least one of R¹⁸ and R¹⁹ represents S(O)_tR³² or SO₂NR³³R³⁴) or C1 to 3 alkyl substituted by SO₂R³⁹.
- 10 In another embodiment, G² represents an optionally substituted bicyclic ring system in which each of the two rings is independently selected from:
- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 15 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;
- 20 and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂.
- In one embodiment, R¹ in formula (I) represents H; G¹ represents phenyl; R⁵ represents halogen, C1 to 6 alkyl, CN or C1 to 3 alkyl substituted by one or more F atoms; R⁴ represents H; L represents C1 to 6 alkyl; and G² represents an optionally substituted monocyclic ring system selected from:
- i) phenyl,

- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group.

In another aspect, the invention specifically provides any compound as described in the Examples herein, or the free base thereof or a pharmaceutically acceptable salt thereof.

10 Particular compounds include:

N-(4-chlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

4-(3-cyanophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide;

15 4-(3-chlorophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide;

4-(3-methylphenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide;

N-[4-(methylsulfonyl)benzyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-

20 dihydroquinoxaline-2-carboxamide;

N-(cyclohexylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

25 3-oxo-N-(pyridin-3-ylmethyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

3-oxo-N'-phenyl-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carbohydrazide;

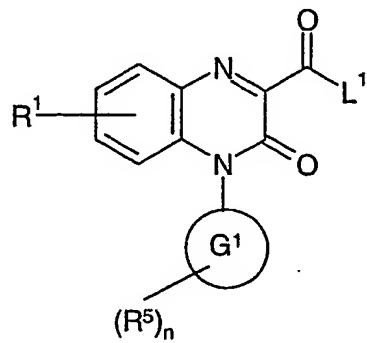
N-(3-bromobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

30 N-(4-bromobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

- 3-oxo-N-[(2R)-2-phenylcyclopropyl]-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-[2-(3-chlorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 5 N-[(4-cyanocyclohexyl)methyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(1-naphthylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(4-methylbenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 10 N-(1,3-benzodioxol-5-ylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(2,4-dichlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 15 N-(4-methoxybenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(3,4-difluorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(2-chloro-4-fluorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 20 N-(3,4-dichlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-[2-(3-methoxyphenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 25 N-[2-(4-fluorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-[1-(4-chlorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 30 3-oxo-N-[3-(2-oxopyrrolidin-1-yl)propyl]-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 3-oxo-N-(pyridin-4-ylmethyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;

- N-(2,3-dihydro-1-benzofuran-5-ylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- methyl 4-{{3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxalin-2-yl}carbonyl}amino]methyl}benzoate;
- 5 3-oxo-N-(4-phenoxybenzyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-{2-[4-(aminosulfonyl)phenyl]ethyl}-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 3-oxo-N-[4-(1H-pyrazol-1-yl)benzyl]-4-[3-(trifluoromethyl)phenyl]-3,4-
- 10 dihydroquinoxaline-2-carboxamide;
- 3-oxo-N-phenoxy-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-[3-(4-methoxyphenyl)isoxazol-5-yl]methyl}-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(3-azepan-1-ylpropyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-
- 15 carboxamide;
- N-[4-(acetylamino)benzyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- N-(4-cyanobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- 20 N'-[4-(methylsulfonyl)phenyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carbohydrazide;
- N-[4-(methylsulfonyl)phenoxy]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide;
- and pharmaceutically acceptable salts thereof.
- 25 The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and
- 30 purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

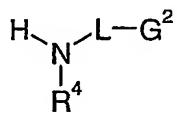
In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II)



(II)

5

wherein R¹, R⁵, G¹ and n are as defined in formula (I) and L¹ represents a leaving group, with an amine of formula (III) or a salt thereof



(III)

10

wherein R⁴, G² and L are as defined in formula (I),

15

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

The process is carried out at a suitable temperature, generally between 0 °C and the boiling point of the solvent, in a suitable solvent such as dichloromethane or NMP

(N-methylpyrrolidinone). The process is optionally carried out in the presence of a base and/or a coupling reagent such as HATU, HOAT, HOBT or DIEA. Suitable leaving groups L¹ include OH and halogen, particularly OH.

- 5 Compounds of formula (II) wherein L¹ represents OH may be prepared using methods that will be readily apparent to the man skilled in the art. See, for example, Hyrayama Takashi et al., J. Chem. Soc. Perkin Trans. 1, 1987, 75-84.

Salts of compounds of formula (I) may be formed by reacting the free base or a salt, 10 enantiomer, tautomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble, or in a solvent in which the salt is soluble followed by subsequent removal of the solvent *in vacuo* or by freeze drying. Suitable solvents include, for example, water, dioxane, ethanol, 2-propanol, tetrahydrofuran or diethyl ether, or mixtures thereof. The 15 reaction may be a metathetical process or it may be carried out on an ion exchange resin.

Compounds of formula (I) and intermediate compounds thereto may be prepared as such or 20 in protected form. The protection and deprotection of functional groups is, for example, described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

25

The compounds of formula (I) may exist in enantiomeric or diastereoisomeric forms or mixtures thereof, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation or HPLC. Alternatively, the

individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions that will not cause racemisation.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified
5 enantiomers, diastereomers, racemates or mixtures thereof.

According to a further aspect of the invention we provide a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

10 The compounds of formula (I), and their pharmaceutically acceptable salts, are useful because they possess pharmacological activity in animals. The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of human neutrophil elastase and homologous serine proteases such as proteinase 3 and pancreatic elastase, and as such are predicted to be useful in therapy. The compounds of formula (I) are particularly useful as
15 inhibitors of human neutrophil elastase. They may thus be used in the treatment or prophylaxis of inflammatory diseases and conditions.

Examples of these conditions are: adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD) and
20 ischaemic-reperfusion injury. The compounds of this invention may also be useful in the modulation of endogenous and/or exogenous biological irritants which cause and/or propagate atherosclerosis, diabetes, myocardial infarction; hepatic disorders including but not limited to cirrhosis, systemic lupus erythematosus, inflammatory disease of lymphoid origin, including but not limited to T lymphocytes, B lymphocytes, thymocytes;
25 autoimmune diseases, bone marrow; inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout); inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis, pancreatitis and gastritis); inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as
30 osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); diseases associated with aberrant angiogenesis; the enhanced collagen remodelling

associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); age related illness such as dementia, inflammatory diseases of

- 5 cardiovascular origins; granulomatous diseases; renal diseases including but not limited to nephritis and polyarteritis; cancer; pulmonary hypertension, ingested poisons, skin contacts, stings, bites; asthma; rhinitis; HIV disease progression; for minimising the effects of organ rejection in organ transplantation including but not limited to human organs; and replacement therapy of proteinase inhibitors.

10

Thus, another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or conditions in which inhibition of neutrophil elastase activity is beneficial; and a method of treating, or reducing the risk of, diseases or

- 15 conditions in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 20 In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of inflammatory diseases or conditions; and a method of treating, or reducing the risk of, inflammatory diseases or conditions which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 25 In particular, the compounds of this invention may be used in the treatment of adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma, rhinitis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, cancer, atherosclerosis and gastric mucosal injury.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or

- 5 those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dose of the compound to be administered will depend on the compound employed, the disease being treated, the mode 10 of administration, the age, weight and sex of the patient. Such factors may be determined by the attending physician. However, in general, satisfactory results are obtained when the compounds are administered to a human at a daily dosage of between 0.1 mg/kg to 100 mg/kg (measured as the active ingredient).

15 The compounds of formula (I) may be used on their own, or in the form of appropriate pharmaceutical formulations comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse reaction, for example, an allergic reaction. Conventional procedures for the selection and preparation of suitable 20 pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

According to the invention, there is provided a pharmaceutical formulation comprising preferably less than 95% by weight and more preferably less than 50% by weight of a 25 compound of formula (I) in admixture with a pharmaceutically acceptable diluent or carrier.

We also provide a method of preparation of such pharmaceutical formulations that comprises mixing the ingredients.

The compounds may be administered topically, for example, to the lungs and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, for example, by oral administration in the form of tablets, pills, capsules, syrups, powders or granules; or by parenteral administration, for example, in the form of sterile parenteral solutions or suspensions; or by rectal administration, for example, in the form of suppositories.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention 10 may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 µm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other 15 pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

20 One possibility is to mix the finely divided compound with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or an other polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be 25 coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug 30 reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a

dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier,
5 for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be
10 coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with, for
15 example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for
20 example, solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

25 The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The following Examples are intended to illustrate, but in no way limit the scope of the invention.

General procedures

- ¹H NMR spectra were recorded on a Varian *Mercury*-VX 300 MHz instrument. The central peak of dimethylsulfoxide-*d*₆ (δ_H 2.50 ppm) was used as internal reference. Column chromatography was carried out using silica gel (0.040-0.063 mm, Merck).
- 5 Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received. Unless otherwise stated, organic solutions were dried using anhydrous Na₂SO₄.
- LC-MS Conditions : Instrument Agilent 1100; Column: Waters Symmetry 2.1 x 30 mm; C18 3.5 μ m; Mass APCI; Flow rate 0.7 ml/min; Wavelength 254 nm; Solvent A: water +
- 10 0.1% TFA; solvent B: acetonitrile + 0.1% TFA ; Gradient 15-95%/B 8 min, 95% B 1 min.
- retention times (RT) are recorded in minutes.

The following abbreviations are used:

- HATU O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
- 15 HOAT 1-Hydroxy-7-azabenzotriazole
- DIEA N,N-Diisopropylethylamine
- NMP 1-N-Methyl-2-pyrrolidinone

Example 1.1 N-(4-Chlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

- a) 3-Oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxylic acid
The title compound was prepared using the general method described by Hyrayama Takashi et al, J. Chem. Soc. Perkin Trans. 1, 1987, 75-84.
- 25 ¹H NMR (DMSO-d₆): δ 14.03 (1H, s); 8.06-7.80 (5H, m); 7.56 (1H, t); 7.44 (1H, t); 6.62 (1H, d).

- b) N-(4-Chlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide
A mixture of 3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxylic acid (94 mg, 0.28 mmol), HATU (122 mg, 0.32 mmol), HOAT (44 mg, 0.32 mmol) and DIEA (138 μ l, 0.78 mmol) in NMP (3 ml) were added to 4-chlorobenzylamine (40 mg,

0.28 mmol) in NMP (2 ml). The reaction mixture was stirred for 18 h. The reaction was diluted with water (8 ml) and purified using preparative HPLC to give the title compound (63 mg, 49%).

¹H NMR (DMSO-d₆): δ 9.35 (1H, t); 8.04-7.90 (4H, m); 7.80 (1H, d); 7.57 (1H, t); 7.45 (1H, t); 7.41 (2H, s); 6.62 (1H, d); 4.51 (1H, d).

Example 1.2 4-(3-Cyanophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

10 a) 4-(3-Cyanophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid

The title compound was prepared using the general method described by Hyrayama Takashi et al, J. Chem. Soc. Perkin Trans. 1, 1987, 75-84.

¹H NMR (DMSO-d₆): δ 14.04 (1H, s); 8.11 (2H, m); 7.95 (1H, d); 7.89 (2H, m); 7.56 (1H, t); 7.45 (1H, t); 6.65 (1H, d).

15 b) 4-(3-Cyanophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

The title compound was prepared by a method analogous to that described in Example 1.1.

¹H NMR (DMSO-d₆): δ 9.45 (1H, t); 8.11 (2H, dt); 7.99 (1H, dd); 7.94-7.82 (4H, m); 7.64 (2H, d); 7.57 (1H, dt); 7.46 (1H, dt); 6.68 (1H, d); 4.63 (2H, d); 3.20 (3H, s).

20

Example 1.3 4-(3-Chlorophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

a) 4-(3-Chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid

25 The title compound was prepared using the general method described by Hyrayama Takashi et al, J. Chem. Soc. Perkin Trans. 1, 1987, 75-84.

¹H NMR (DMSO-d₆): δ 14.04 (1H, s); 7.94 (1H, d); 7.70 (3H, m); 7.56 (1H, t); 7.52-7.38 (2H, t); 6.66 (1H, d).

b) 4-(3-Chlorophenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

30 The title compound was prepared by a method analogous to that described in Example 1.1.

¹H NMR (DMSO-d₆): δ 9.45 (1H, t); 7.97 (1H, d); 7.91 (2H, d); 7.77-7.51 (6H, m); 7.45 (2H, m); 6.68 (1H, d); 4.63 (2H, d); 3.20 (3H, s).

Example 1.4 4-(3-Methylphenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

a) 4-(3-Methylphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid

The title compound was prepared using the general method described by Hyrayama Takashi et al, J. Chem. Soc. Perkin Trans. 1, 1987, 75-84.

¹⁰ ¹H NMR (DMSO-d₆): δ 14.04 (1H, s); 7.93 (1H, dd); 7.55 (2H, m); 7.43 (2H, m); 7.25 (2H, d); 6.64 (1H, d); 2.41 (3H, s).

b) 4-(3-Methylphenyl)-N-[4-(methylsulfonyl)benzyl]-3-oxo-3,4-dihydroquinoxaline-2-carboxamide

The title compound was prepared by a method analogous to that described in Example 1.1.

¹⁵ ¹H NMR (DMSO-d₆): δ 9.46 (1H, t); 7.96 (1H, d); 7.91 (2H, d); 7.65 (2H, d); 7.56 (2H, t); 7.44 (2H, m); 7.22 (2H, d); 6.64 (1H, d); 4.62 (2H, d); 3.20 (3H, s); 2.41 (3H, s).

Using the appropriate amine or a salt thereof, the following compounds were prepared by a method analogous to that described in Example 1.1.

²⁰ **Example 2.1** N-[4-(Methylsulfonyl)benzyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

¹H NMR (DMSO-d₆): δ 9.44 (1H, t); 8.04-7.87 (6H, m); 7.81 (1H, d); 7.64 (2H, d); 7.57 (1H, dt); 7.46 (1H, dt); 6.64 (1H, d); 4.63 (1H, d); 3.20 (3H, s).

²⁵ **Example 2.2** N-(Cyclohexylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.76 min, m/z 430.2 [MH⁺].

Example 2.3 N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 4.89 min, m/z 498.2 [MH⁺].

5 Example 2.4 3-Oxo-N-(pyridin-3-ylmethyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 3.09 min, m/z 425.1 [MH⁺].

10 Example 2.5 3-Oxo-N'-phenyl-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carbohydrazide

LC-MS RT: 4.90 min, m/z 425.1 [MH⁺].

15 Example 2.6 N-(3-Bromobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.63 min, m/z 502.1 [MH⁺].

20 Example 2.7 N-(4-Bromobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.68 min, m/z 502.1 [MH⁺].

25 Example 2.8 3-Oxo-N-[(2R)-2-phenylcyclopropyl]-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.57 min, m/z 450.2 [MH⁺].

30 Example 2.9 N-[2-(3-Chlorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.68 min, m/z 472.1 [MH⁺].

Example 2.10 N-[(4-Cyanocyclohexyl)methyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 4.79 min, m/z 455.2 [MH⁺].

Example 2.11 N-(1-Naphthylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

5 LC-MS RT: 5.71 min, m/z 474.2 [MH⁺].

Example 2.12 N-(4-Methylbenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.47 min, m/z 438.2 [MH⁺].

10

Example 2.13 N-(1,3-Benzodioxol-5-ylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.05 min, m/z 468.1 [MH⁺].

15 **Example 2.14** N-(2,4-Dichlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.98 min, m/z 492.1 [MH⁺].

20 **Example 2.15** N-(4-Methoxybenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.11 min, m/z 454.2 [MH⁺].

Example 2.16 N-(3,4-Difluorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

25 LC-MS RT: 5.38 min, m/z 460.1 [MH⁺].

Example 2.17 N-(2-Chloro-4-fluorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 476.3 [MH⁺].

Example 2.18 N-(3,4-Dichlorobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 492.2 [MH⁺].

5

Example 2.19 N-[2-(3-Methoxyphenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 6.80 min, m/z 468.4 [MH⁺].

10 **Example 2.20** N-[2-(4-Fluorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 456.3 [MH⁺].

15 **Example 2.21** N-[1-(4-Chlorophenyl)ethyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 472.3 [MH⁺].

20 **Example 2.22** 3-Oxo-N-[3-(2-oxopyrrolidin-1-yl)propyl]-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 459.3 [MH⁺].

25 **Example 2.23** 3-Oxo-N-(pyridin-4-ylmethyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 3.12 min, m/z 425.1 [MH⁺].

25

Example 2.24 N-(2,3-Dihydro-1-benzofuran-5-ylmethyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.10 min, m/z 466.2 [MH⁺].

Example 2.25 Methyl 4-{{[({3-oxo-4-[3-(trifluoromethyl)phenyl]phenyl]-3,4-dihydroquinoxalin-2-yl}carbonyl)amino]methyl}benzoate

LC-MS RT: 5.08 min, m/z 482.2 [MH⁺].

5 **Example 2.26** 3-Oxo-N-(4-phenoxybenzyl)-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 516.3 [MH⁺].

10 **Example 2.27** N-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

APCI-MS m/z: 517.3 [MH⁺].

15 **Example 2.28** 3-Oxo-N-[4-(1H-pyrazol-1-yl)benzyl]-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 4.99 min, m/z 490.2 [MH⁺].

20 **Example 2.29** 3-Oxo-N-phenoxy-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.11 min, m/z 426.1 [MH⁺].

Example 2.30 N-{{[3-(4-Methoxyphenyl)isoxazol-5-yl]methyl}-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 5.40 min, m/z 521.2 [MH⁺].

25 **Example 2.31** N-(3-Azepan-1-ylpropyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 3.50 min, m/z 473.3 [MH⁺].

30 **Example 2.32** N-[4-(Acetylamino)benzyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 4.20 min, m/z 481.2 [MH⁺].

Example 2.33 N-(4-Cyanobenzyl)-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

5 LC-MS RT: 4.94 min, m/z 449.1 [MH⁺].

Example 2.34 N-[4-(Methylsulfonyl)phenyl]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carbohydrazide

LC-MS RT: 4.31 min, m/z 503.1 [MH⁺].

10

Example 2.35 N-[4-(Methylsulfonyl)phenoxy]-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydroquinoxaline-2-carboxamide

LC-MS RT: 4.53 min, m/z 504.1 [MH⁺].

15

Screen

Human Neutrophil Elastase Quenched-FRET Assay

The assay uses Human Neutrophil Elastase (HNE) purified from serum (Calbiochem art.

20 324681; Ref. Baugh, R.J. et al., 1976, Biochemistry. 15, 836-841). HNE was stored in 50 mM NaOAc, 200 mM NaCl, pH 5.5 with added 30% glycerol at -20 °C. The protease substrate used was Elastase Substrate V Fluorogenic, MeOSuc-AAPV-AMC (Calbiochem art. 324740; Ref. Castillo, M.J. et al., 1979, Anal. Biochem. 99, 53-64). The substrate was stored in DMSO at -20 °C. The assay additions were as follows: Test compounds and 25 controls were added to black 96-well flat-bottom plates (Greiner 655076), 1 µL in 100% DMSO, followed by 30 µL HNE in assay buffer with 0.01% TritonX-100. The assay buffer constitution was: 100 mM Tris (pH 7.5) and 500 mM NaCl. The enzyme and the compounds were incubated at room temperature for 15 minutes. Then 30 µL substrate in assay buffer was added. The assay was stopped after 30 minutes incubation at room

temperature by adding 60 μ l stop solution (140 mM acetic acid, 200 mM sodium monochloroacetate, 60 mM sodium acetate, pH 4.3). Fluorescence was measured on a Wallac 1420 Victor 2 instrument at settings: Excitation 380 nm, Emission 460 nm. IC₅₀ values were determined using Xlfit curve fitting using model 205.

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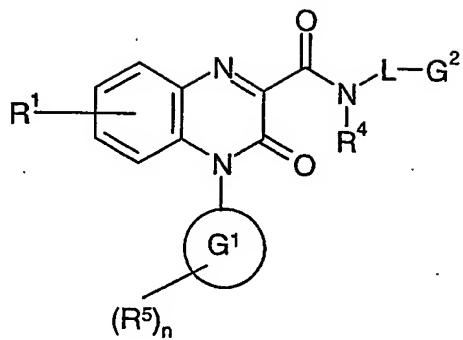
When tested in the above screen, the compounds of the Examples gave IC₅₀ values for inhibition of human neutrophil elastase activity of less than 30 μ M, indicating that the compounds of the invention are expected to possess useful therapeutic properties. Specimen results are shown in the following Table:

10

Compound	Inhibition of Human Neutrophil Elastase IC ₅₀ (nM)
Example 2.12	226
Example 2.10	248
Example 2.20	573

Claims

1. A compound of formula (I)



5

(I)

wherein

R^1 represents H, halogen, CN, C1 to 6 alkyl, C1 to 6 alkoxy, CO_2R^7 or $CONR^8R^9$;

10

G^1 represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N;

15

R^5 represents H, halogen, C1 to 6 alkyl, CN, C1 to 6 alkoxy, NO_2 , $NR^{14}R^{15}$, C1 to 3 alkyl substituted by one or more F atoms or C1 to 3 alkoxy substituted by one or more F atoms;

R^{14} and R^{15} independently represent H or C1 to 3 alkyl; said alkyl being optionally further substituted by one or more F atoms;

20 n represents an integer 1, 2 or 3 and when n represents 2 or 3, each R^5 group is selected independently;

R⁴ represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH or C1 to 6 alkoxy;

or R⁴ and L are joined together such that the group -NR⁴L represents a 5 to 7 membered 5 azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR¹⁶;

L represents a bond, O, NR²⁹ or C1 to 6 alkyl; said alkyl being optionally incorporating a heteroatom selected from O, S and NR¹⁶; and said alkyl being optionally further 10 substituted by OH or OMe;

G² represents a monocyclic ring system selected from:

- i) phenyl or phenoxy,
- 15 ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two 20 heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group; or

G² represents a bicyclic ring system in which each of the two rings is independently selected from:

- i) phenyl,
- 25 ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or

- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;
- 5 and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂,
- said monocyclic or bicyclic ring system being optionally further substituted by one to three substituents independently selected from CN, OH, C1 to 6 alkyl, C1 to 6 alkoxy, halogen,
 10 NR¹⁸R¹⁹, NO₂, OSO₂R³⁸, CO₂R²⁰, C(=NH)NH₂, C(O)NR²¹R²², C(S)NR²³R²⁴, SC(=NH)NH₂, NR³¹C(=NH)NH₂, S(O)₈R²⁵, SO₂NR²⁶R²⁷, C1 to 3 alkoxy substituted by one or more F atoms and C1 to 3 alkyl substituted by SO₂R³⁹ or by one or more F atoms; or
 15 when L does not represent a bond, G² may also represent H;
- p, q, s and t independently represent an integer 0, 1 or 2;
- R⁸ and R⁹ independently represent H or C1 to 6 alkyl; or the group NR⁸R⁹ together
 20 represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR²⁸;
- R¹⁸ and R¹⁹ independently represent H, C1 to 6 alkyl, formyl, C2 to 6 alkanoyl, S(O)_tR³²
 or SO₂NR³³R³⁴; said alkyl group being optionally further substituted by halogen, CN,
 25 C1 to 4 alkoxy or CONR⁴¹R⁴²;
- R²⁵ represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally further substituted by one or more substituents selected independently from OH, CN,

CONR³⁵R³⁶, CO₂R³⁷, OCOR⁴⁰, C3 to 6 cycloalkyl, a C4 to 7 saturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR⁴³ and phenyl or a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N; said aromatic ring being optionally further substituted by one or more substituents selected independently from halogen, CN, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CONR⁴⁴R⁴⁵, CO₂R⁴⁶, S(O)_sR²⁵ or NHCOCH₃;

R³² represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl;

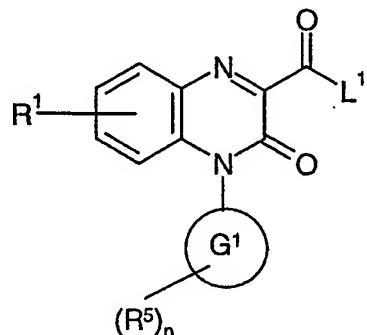
10 R⁷, R¹⁶, R¹⁷, R²⁰, R²¹, R²², R²³, R²⁴, R²⁶, R²⁷, R²⁸, R²⁹, R³¹, R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶ independently represent H or C1 to 6 alkyl;

and pharmaceutically acceptable salts thereof.

- 15 2. A compound of formula (I), according to Claim 1, wherein G¹ represents phenyl.
3. A compound of formula (I), according to Claim 1 or Claim 2, wherein R⁴ represents H.
- 20 4. A compound of formula (I), according to any one of Claims 1 to 3, wherein R⁵ represents Cl, CH₃, CN or CF₃.
5. A compound of formula (I), according to any one of Claims 1 to 4, or a
25 pharmaceutically acceptable salt thereof, for use as a medicament.
6. A pharmaceutical formulation comprising a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable diluent or carrier.

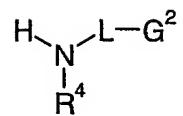
7. A method of treating, or reducing the risk of, a human disease or condition in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a person suffering from or susceptible to such a disease or condition, a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof.
8. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of neutrophil elastase activity is beneficial.
9. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of inflammatory diseases or conditions.
10. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 4, and optical isomers, racemates and tautomers thereof and pharmaceutically acceptable salts thereof, which comprises reacting a compound of formula (II)

20



(II)

wherein R¹, R⁵, G¹ and n are as defined in Claim 1 and L¹ represents a leaving group, with an amine of formula (III) or a salt thereof



(III)

wherein R^4 , G^2 and L are as defined in Claim 1,

- 5 and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001225

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 241/44, C07D 403/12, C07D 413/12, A61K 31/498, A61P 29/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0008864 A1 (FISONS LIMITED), 19 March 1980 (19.03.1980) --	1-10
X	STN International, File CAPLUS, CAPLUS accession no. 1995: 456529, Document no. 123:198678, Ukrainets, I.V. et al: '4-Hydroxy-2-quinolones. 23. N-(2-Thiazolyl)amides of 1-substituted 4-hydroxy-2-oxoquinoline-3-carboxylic acids - a new group of potential antiinflammatory drugs'; & Khimiya Geterotsiklichesikh Soedinenii (1994), (10), 1397-9 --	1-10

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 December 2004

Date of mailing of the international search report

15-12-2004

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001225

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1990:611864, Document no. 113:211864, Otsuka Pharmaceutical Co., Ltd.: '4-Hydroxycarbostyrils as antiinflammatory and antiallergy agents'; & JP,A2,02152966, 19900612 -----	1-10

INTERNATIONAL SEARCH REPORTInternational application No.
pct/SE2004/001225**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
See next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
pct/SE2004/001225

Box 2.1

Claim 7 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Inte	rnal application No.
PCT/SE 2004/001225	

EP	0008864 A1	19/03/1980	AU	4985379 A	21/02/1980
			DK	338379 A	16/02/1980
			ES	483398 A	01/09/1980
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			GR	69706 A	09/07/1982
			IL	58038 D	00/00/0000
			JP	55115875 A	06/09/1980
			NO	792653 A	18/02/1980
			PT	70064 A	01/09/1979
			US	4296114 A	20/10/1981
			ZA	7904209 A	30/07/1980

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